Effects of BCAA Enteral Nutrition to the Change of Nutritional Status and Hepatic Encephalopathy Parameters in Liver Cirrhosis Patient with Hepatic Encephalopathy

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ABSTRACT

Background: *This study was also conducted to determine the effects of high-branched chain amino acid (BCAA) enteral supplementation on altered nutritional status parameters (including plasma prealbumin) and hepatic encephalopathy parameters in liver cirrhosis patients with hepatic encephalopathy.*

Method: *Our study was a randomized, single-blinded experimental study comparing between control group of liver cirrhosis patients with standard hospital liver diet (40 kcal/kgBW/day for male and 35 kcal/kgBW/day for female; protein 1.25 g/kgBW/day) and experimental group of liver cirrhosis patients with liver diet modification high in BCAA supplementation, which had similar protein and calorie calculation as the control group.*

Results: *Subclinical hepatic encephalopathy prevalence was 32%. In the experimental group, prealbumin plasma, arm circumference, body weight and body mass index (BMI) increased; whereas in the control group, prealbumin plasma, arm circumference, body weight and BMI decreased ($p < 0.05$). In experimental group, the ammonia level significantly decreased ($p < 0.01$). Clinical hepatic encephalopathy, flapping tremor, the number connection test (NCT) did not show significant changes between the two groups. However, there was worsening trend in the control group. Level of albumin, bilirubin, AST, ALT did not show any significant difference between both groups.*

Conclusion: *High-BCAA enteral supplementation which is administered to liver cirrhosis patients with hepatic encephalopathy for 14 days could improve plasma prealbumin level, arm circumference, body weight, BMI and could decrease the plasma ammonia level. However, it does not improve Fischer ratio, psychometric test and electroencephalography*

Keywords: *malnutrition, liver cirrhosis, BCAA, Fisher ratio*

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INTRODUCTION

In 1971, specific amino acid treatment came into therapeutic arena for liver cirrhosis patients, i.e. when Fischer and Baldessarini first introduced the association between hepatic encephalopathy an imbalance of plasma amino acid through false neurotransmitter synthesis.[1,2] Since that time, many studies, both

clinically and experimentally, had been conducted to confirm their hypothesis, as well as an effort to improve mental status through amino acid supplementation. However, after three decades pass by, the problem remains unsolved. Nevertheless, a lot of information has been collected related to metabolism of energy, amino acids and protein in liver cirrhosis patients.

Hepatic encephalopathy (HE) is a neuro-psychiatric syndrome that only occur in a significant liver dysfunction condition. It can be caused by various clinical conditions such as congenitally urea cycle disorders, acute or chronic liver diseases, spontaneous/iatrogenic portosystemic venous shunting, including after the placement of transjugular intrahepatic portosystemic shunt (TIPS).[1,2]

HE may occur in 50-70% of liver cirrhosis patients, including the abnormality than can only be assessed by psychometric test.[2] Data based on hospital care unit reveals that there was 1.34-14.5% of patients with liver disease, and 20-73.8% of them had liver cirrhosis.[3] Clinical manifestation of hepatic encephalopathy varied from imperceptible clinical symptoms (e.g. subclinical hepatic encephalopathy, that can only be detected by psychometric test) to deep coma. Subclinical hepatic encephalopathy identified by electrophysiologic abnormalities and psychometric test. Since the level of consciousness is not disturbed, it is difficult to assess the clinical impact of subclinical hepatic encephalopathy. However, a clinical relation had been reported with respect to decreased ability of driving and deterioration in quality of life.[1]

An important factor explaining the pathogenesis of hepatic encephalopathy is the role of branched-chain amino acid (BCAA) ratio or aromatic amino acids (AAA) ratio. Some studies that evaluate benefit of BCAA therapy in liver cirrhosis patients and hepatic encephalopathy give varied results.[2-17] In general, BCAA has protein sparing effect.[6,13] BCAA effect on hepatic encephalopathy has to be clarified.

Prealbumin is one of indicators for nutritional status. The half-life of prealbumin metabolism is 1-2 days, and half-life of albumin and transferrin are longer (7-21 days); while, the half-life of retinol binding protein is very short (10 hours).[18-20] Foreign literatures demonstrate that studies concerning on the effects of BCAA supplementation are especially related to alcoholic liver-cirrhosis patients. In contrast, only few studies in non-alcoholic liver cirrhosis has been reported. This study was done to determine the effects of high enteral BCAA supplementation on altered nutritional status parameters (including plasma prealbumin) and hepatic encephalopathy parameters.

METHOD

This study was conducted on February 1998 till August 2000 at Division of Hepatology, Department of Internal Medicine, Cipto Mangunkusumo hospital. It was a randomized, single-blinded experimental study comparing between control group of liver cirrhosis patients with standard hospital liver diet (40 kcal/kgBW/day for male and 35 kcal/kgBW/day for female; protein 1.25 g/kgBW/day) and experimental group of liver cirrhosis patients with liver diet modification high in BCAA supplementation, which had similar protein and calorie calculation as the control group. Such method was utilized to determine the effects of high-BCAA enteral supplementation on altered nutritional status parameters (including plasma prealbumin) and hepatic encephalopathy parameters.

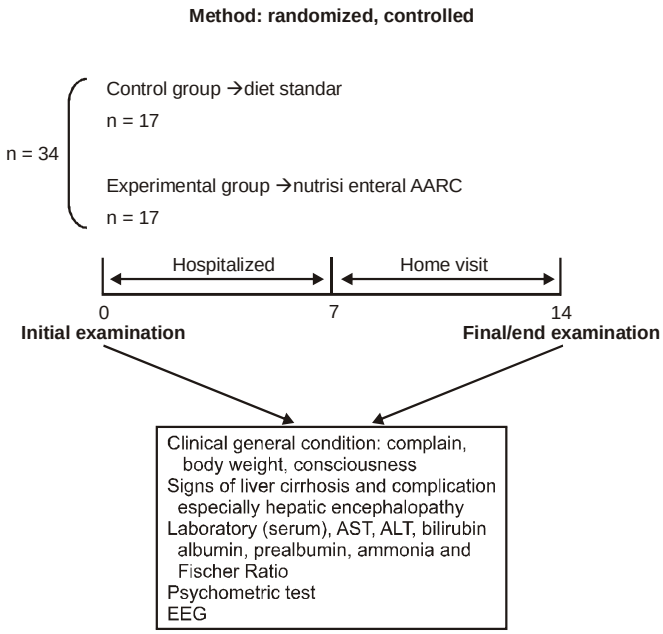

Figure 1. Method illustration of this randomizedcontrolled clinical trial

RESULTS

Thirty-four eligible liver cirrhosis patients were included (17 patients in the control group and 17 patients in the experimental group) in this study (table 1).

There were no significant difference in charac-teristics of both groups according to age distribution, gender, Child-Pugh classification, level of education and viral etiology. Results of clinical data, psychometric test, initial and end of electroen-cephalography (EEG) in both groups were showed on table 2 and 3.

Tabel 1. Patient characteristics in both groups

Characteristic	Experimental	Control	p
	n (%)	n (%)	
Gender			> 0.05$^{\pi}$
Male	11 (64.7)	10 (58.8)	
Female	6 (35.3)	7 (41.2)	
Education			> 0.05$^{\pi}$
Uneducated	1 (5.9)		
Elementary school	3 (17.65)	4 (23.5)	
Secondary school	3 (17.65)	1 (5.9)	
Tertiary school	5 (29.4)	8 (47.1)	
College	5 (29.4)	4 (23.5)	
Child Pugh			> 0.05$^{\pi}$
A	8 (47.1)	10 (58.8)	
B	5 (29.4)	6 (35.3)	
C	4 (23.5)	1 (5.9)	
Viral etiology			> 0.05$^{\pi}$
Non B non C	3 (17.65)	2 (11.8)	
B	3 (17.65)	4 (23.5)	
C	11 (64.7)	9 (52.9)	
B & C		2 (11.8)	
Age (year)			> 0.05$^{\tau}$
Mean ± SD	56.24 ± 8.29	56.82 ± 7.27	

Note: π = Pearson chi-square test; τ = t-test for independent samples;
SD = standard deviation

Table 2. Clinical data, psychometric test and initial and end of EEG in both groups

	Experimental		Control	
	Initial n (%)	End n (%)	Initial n (%)	End n (%)
Hepatic encephalopathy				
None	3 (17.6)	5 (29.4)	8 (47.1)	7 (41.2)
Grade I	12 (70.6)	12 (70.6)	8 (47.1)	9 (53)
Grade II	2 (11.8)	0	1 (5.8)	1 (5.8)
Flapping tremor				
None	12 (70.6)	13 (76.5)	11 (64.7)	9 (53)
Grade I	5 (29.4)	4 (23.5)	6 (35.3)	7 (41.2)
Grade II	0	0	0	1 (5.8)
Number connection test (second)				
Grade I = 31-50	4 (23.5)	7 (41.2)	5 (29.4)	7 (41.2)
Grade II = 51-80	10 (58.9)	7 (41.2)	6 (35.3)	6 (35.3)
Grade III = 81-120	2 (11.7)	2 (11.7)	5 (29.4)	3 (17.6)
Grade IV ? 120	1 (5.9)	1 (5.9)	1 (5.9)	1 (5.9)
Ammonia (nmol/L)				
Normal ? 45	2 (11.8)	7 (41.2)	6 (35.3)	7 (41.2)
Grade 1= 45 - 60	5 (29.3)	2 (11.8)	4 (23.5)	7 (41.2)
Grade 2 = 61 - 75	1 (5.9)	3 (17.6)	4 (23.5)	0
Grade 3 = 76 - 90	2 (11.8)	2 (11.8)	1 (5.9)	0
Grade 4 $\geq$ 90	7 (41.2)	3 (17.6)	2 (11.8)	3 (17.6)
Ascites				
None	13	15	12	17
Mild	2	2	5	0
Moderate	2	0	0	0
EEG				
Normal	12 (70.6)	13 (76.5)	13 (76.5)	14 (82.4)
Grade 2	5 (29.4)	4 (23.5)	4 (23.5)	3 (17.6)

Note: Initial = before experimental study proceed (beginning); End = after experimental study was done for 14 days (end of study); EEG: Electroencephalography

Table 3. Laboratory and psychometric test results at the beginning and end of study in both groups

Parameter	Experimental		Control		ρ_τ
	Initial	End	Initial	End	
	$\chi \pm SD$	$\chi \pm SD$	$\chi \pm SD$	$\chi \pm SD$	
Arm circumference (cm)	20.06 ± 11.62	20.12 ± 11.66	24.85 ± 9.97	24.75 ± 9.96	0.035
Body weight (kg)	55.68 ± 7.13	56.21 ± 6.91	58.76 ± 12.87	58 ± 12.71	0.041
Body mass index	21.80 ± 3.13	22.02 ± 3.18	23.50 ± 4.51	23.14 ± 4.26	0.031
Number connection test (second)	69.29 ± 29.59	64.41 ± 35.77	71.41 ± 27.17	67.18 ± 27.56	0.921
AST (U/L)	45.12 ± 25.37	41.53 ± 34.32	36.41 ± 35.57	35.53 ± 33.12	0.775
ALT (U/L)	29.71 ± 17.56	25.94 ± 16.82	24.41 ± 17.75	25.12 ± 26.04	0.486
Total bilirubin (mg/dL)	1.53 ± 1.49	1.12 ± 0.93	1.05 ± 0.63	0.92 ± 0.5	0.320
Direct bilirubin (mg/dL)	0.84 ± 0.88	0.59 ± 0.56	0.48 ± 0.35	0.49 ± 0.38	0.064
Albumin (g/dL)	3.32 ± 1.09	3.24 ± 1.12	3.35 ± 1.16	3.23 ± 0.93	0.905
Globulin (g/dL)	3.34 ± 1.07	3.27 ± 1.12	3.39 ± 1.62	3.24 ± 1.15	0.782
Prealbumin (g/L)	0.11 ± 0.049	0.12 ± 0.054	0.14 ± 0.079	0.14 ± 0.063	0.016
Plasma ammonia (nmol/L)	88.41 ± 50.04 *	64.47 ± 37.39 *	71.24 ± 51.26	55.29 ± 24.97	0.577
Fischer ratio (χ/M/κ)	3.36/1.97/ 0.42-20.45	3.87/1.54/ 0.23-16.73	2.31/1.97/ 0.40-9.28	2.69/1.84/ 0.16-11.11	0.951

Note: Initial: before experimental study proceed (beginning); end: after study was done for 14 days (end of study); SD: standard deviation; M: median; κ: range minimum-maximum: mean; τ: t-test for independent samples; (*): t test for pair group $p < 0.01$

Grade of Clinical Hepatic Encephalopathy

Statistic test of Pearson Chi-square showed significant difference between both groups (p = 0.033). On the contrary, the Fisher's exact test did not show significant difference between both groups (p = 0.103).

Table 4. Altered grading of hepatic encephalopathy in both groups

	Worsen/no change	Improved
Experimental	13	4
Control	17	0

Note: Pearson Chi-square test p = 0.033; RRR = 0.24; ARR = 0.24 Fisher's exact test p = 0.103; NNT = 4; CI 95%

Table 5. Altered grading of flapping tremor in both groups

	Worsen/no change	improved
Experimental	16	1
Control	15	2

Note: Pearson Chi-square test, p = 0.545; Fisher's exact test p = 1.00

Flapping Tremor

In the experimental group, no worsening grading of flapping tremor was found. However, in the control group, there were five patients got worse condition.

Psychometric Test/Number Connection Test

In both experimental and control groups, there were no patient had number connection test (NCT) grade 0. Thus, our study found hepatic encephalopathy in all patients with liver cirrhosis. Statistic test with Pearson Chi-square (p = 0.067) and Fisher's exact (p = 0.141) did not show any significant difference between both groups.

Table 6. Altered grading of NCT in both groups

	Worsen/no change	Improved
Experimental	3	14
Control	8	9

Note: Pearson Chi-square test p = 0.067; RRR = 0.63; ARR = 0.29; Fisher's exact test p = 0.141; NNT = 3.4; CI 95%

Electroencephalography

Statistic test between both groups showed no significant difference.

Table 7. Altered grading of EEG in both groups

	No change	Improved
Experimental	16	1
Control	16	1

Note: Pearson Chi-square test, p = 1.00; Fisher's exact test p = 1.00

DISCUSSION

Liver is the main organ in metabolism of carbohydrate, fat, protein, vitamin, mineral and trace element. Liver has important role in protein and amino acids metabolism. Liver processing amino acids that derived from diet or released by skeletal muscles due to protein degradation (catabolism). Liver uses amino acids, particularly for the need of protein synthesis and gluconeogenesis. Liver also regulates amino acids supply for peripheral tissues and changes excessive amino acids into urea. Therefore, in patient with liver cirrhosis, the capability to regulate amino acids, both in plasma as well as tissues could be very disturbed.[13,14,15]

In the early 1980's, it was postulated that hepatic encephalopathy in liver cirrhosis could be improved by giving formulation of protein enriched by BCAA with just few of AAA (phenylalanine, tyrosine, tryptophan). Such opinion is supported by the results of observation on plasma amino acids profile in liver cirrhosis patients, which is characterized by accumulation of AAA and decreased level of gluconeogenic amino acids, especially BCAA. It is well known that BCAA - leucine, isoleucine and valine - are unique amino acids due to their extra hepatic metabolism in skeletal muscles. In muscles, BCAA is available as important energy substrates for exercise, stress period and as precursor of others amino acids synthesis and protein.

Early studies of BCAA were commonly focused on the anabolic effects, especially in conditions of catabolic stress disorders and theoretically potential to prevent or treat encephalopathy in liver failure. Therefore, BCAA was promoted as beneficial supplementation in these patients. However, some similar clinical studies seem to cause decreased interest in nutritional supplementation of BCAA.[13,16,17]

Considering that BCAA is a protein precursor, so becoming a paradox if evaluation of liver disease has only been focused on the effects of mental function and ignoring evaluation of their nutritional effects with only a few studies about therapeutic effects of BCAA on the energy balance which were conducted in the years 1980's to early 1990's.[17]

The main rationalization on BCAA utilization in hepatic encephalopathy patients has becoming wane since its first promotion in 1975. It has shifting to and focusing on their nutritional effects, for example in improving malnutrition, which is common finding in liver cirrhosis patients that greatly determine the prognosis. Potential benefit of leucine, valine and isoleucine in liver cirrhosis patients with malnutrition is an independent effect. It does not depend on therapeutic value of hepatic encephalopathy. BCAA inhibits protein catabolism in muscles. BCAA also increases the synthesis of muscle and liver protein and also available as sources of energy substrates for muscle tissues.

In this study, we evaluate the therapeutic effects of BCAA supplementation on nutritional status, which was represented by plasma prealbumin level and effect of BCAA supplementation to encephalopathy hepatic parameters. Since the half-life of prealbumin metabolism is 1-2 days, prealbumin is regarding to be appropriate for the study; not to mention considering the half-life of albumin and transferrin are too long (7-21 days) or the half-life of retinol-binding protein is too short (10 hours).[18,19,20]

Our study found significant difference in nutritional status parameter between the experimental and control groups. There was increased plasma prealbumin level correlated to increased arm circumferences, body weight, and BMI in the experimental group. However, the control group demonstrated decreased plasma prealbumin level, arm circumference, body weight or BMI. Such findings supports the facts that the most consistent findings related to BCAA is protein-spare of BCAA in liver cirrhosis patients.[11,13,21-28] Arm circumference is a more accurate parameter in liver cirrhosis patients compared to body weight or BMI, since ascitic fluid does not accumulate in arm circumference. If we measure the triceps skinfold thickness (TST), then by using Bishop formula, we will get the arm muscle circumference (AMC). Both TST and AMC are also accurate anthropometric parameters in liver cirrhosis patients, that can be measured by this calculation: AMC (cm) = AC (cm) – 0.314 x TSF (mm).[11]

We found 11 patients with clinically normal hepatic encephalopathy/grade 0; while the results of psychometry test revealed no one as normal on NCT, so there were 32% of patients with sub-clinical hepatic encephalopathy. In the literatures, the prevalence of hepatic encephalopathy is around 20–84%.[29-31]

Several studies found significant improvement of clinical hepatic encephalopathy after supplementation of high BCAA diet.[5,7,32,33] However, some others studies and a metaanalysis study did not found benefit of BCAA supplementation in hepatic encephalopathy nor improved mortality rate of hepatic encephalopathy patients.[11,34,35] In this study, we found no significant improvement of hepatic encephalopathy. However, data's showed that there is a trend of improvement in the experimental group compare to the control group which have worsening trend. In the experimental group, four patients had improvement in clinical hepatic encephalopathy grading and no one got deteriorate. Meanwhile, in the control group, there is no one got improvement and one patient got worsening condition.

Psychometric test is a tool to assess the presence of neuropsychiatry disturbances in liver cirrhosis patients. Several studies showed that BCAA supplementation could improve psychometric test significantly.[9,32,33] However, it was known that result of psychometric test is very much influenced by certain factors including learning/training effect, educational status, mind perception, intellectuality, level of intelligent, the need for age-matched controls, etc.[30,36] In this study, there is no significant difference between both groups. However, there were more patients (14 patients) who had improved NCT in the experimental group compared to the control group (9 patients), and there were more patients (7 patients), who got worsen NCT in the control group compared to the experimental group (3 patients).

Flapping tremor is also one of hepatic encepha lopathy signs. As well as NCT, in this study, there is no significant difference between both groups. However, in the control group, we found 5 patients with deterioration; while in the experimental group, there were no one got deteriorated. Such finding is different from other studies that found significant improvement in flapping tremor grading with high-BCAA supplementation

EEG is considered could give more objective result than psychometric test in assessing hepatic encephalopathy since it does not depend on age and educational status and does not show learning effect on repeated examination. However, its diagnostic sensitivity is lower than psychometric test.[29,36] Some

of EEG limitations are insensitive in deep brain activity, changes related to age and change in conditions such as level of alertness or drowsiness and individual different variabilities.[37] In this study, there is no significant difference on EEG changes between the control and experimental groups. Higuchi et al found a significant prolonged latent P3 wave by evoked potential examination in liver cirrhosis patients compared to control group.[33]

Metabolism disturbance in liver cirrhosis could decrease Fischer ratio. In this study, Fisher ratio mostly less than 3 (70%) with values range of 0.1606–20.4509. Supplementation of high-BCAA diet could improve Fisher ratio significantly.[6,38] This study does not demonstrate significant increase of Fisher ratio between the experimental and control groups, although there is increased Fisher ratio in both groups. Variation of Fisher ratio values could occur since the amino-acids turn over is very dynamic. Thus, the high or low plasma amino acids level does not always reflect the utilization of such amino acids. Besides that, there were other factors influencing contents of amino acids in plasma, such as duration of fasting, variability of timing to get blood samples or patient metabolism status. Kinetic studies is more appropriate in reflecting amino acids utilization.[21,39]

Effects of supplementation of high-BCAA diet on plasma ammonia level is various. Several studies showed decreased plasma ammonia level after giving high-BCAA diet due to increased clearance of blood ammonia.[33,40] In this study, we found decreased plasma ammonia level, both in the experimental and control groups. Although there is no significant difference between both groups; however, decreased plasma ammonia level in the experimental groups before and after treatment showed significant difference.

Our study also demonstrates no significant differences between both groups regarding changes in level of albumin, globulin, AST and ALT. In this study, even there is no significant difference between both groups and no significant difference amongst each group, but albumin level in both groups decreased. Such phenomenon is a more reflecting condition of pre-study considering the half-life of albumin is very long (21 days) due to large albumin pool size. Therefore, the fluctuation of albumin turnover will not immediately reflected in plasma albumin level. Albumin is not a sensitive indicator for nutritional status parameter, particularly to assess alteration in short-time period.

In this study, nutritional status parameters provided more significant result compared to hepatic encephalopathy parameters. However, hepatic encephalopathy parameters showed a tendency of improvement in the experimental group. This could be occurred considering that factors influencing hepatic encephalopathy parameters are more variable and it is affected not only by protein/BCAA supplementation. These will influence the study results, considering that patients in this study are mostly ambulatory.

Although the effort of nutritional supervision has been conducted strictly enough; however, control on others factors that can influence to hepatic encephalopathy are hardly enough to be done, e.g. different defecation habit pattern among patients, the occurrence and absence of constipation, antibiotic consumption at home, laxative consumption, the presence of occult bleeding, electrolytes disturbances, etc. In future studies, all patients should be hospitalized and strictly monitored, so that the BCAA supplementation will be the only factor to be assessed that affect both experimental and control groups. In addition, to observe better results in hepatic encephalopathy parameters, the treatment should be proceed in longer duration than this study (14 days) and with larger samples.

BCAA supplementation provides benefit and it could be well-tolerated by almost all patients, there was only 1 patients suffering diarrhea and could not complete the study. Limitation in utilizing BCAA supplementation right now in liver cirrhosis patients is the expensive cost.

Branched-chain amino acids (BCAA), i.e. leucine, isoleucine and valine are essential amino acids that cannot be produced by the body. In fact, it must be obtained from diet, and primarily metabolized by muscle mass rather than by liver. The use of BCAA remains controversial and they are not widely available in many centers due to their expense and unpalatability. The European Society on Parenteral and Enteral Nutrition Guidelines recommends that enteral feed enriched with BCAA should be reserved for patients who develop encephalopathy with enteral feeding despite appropriate treatment. This represents a very small proportion of patients.[41,42,43,44]

CONCLUSION

High-BCAA enteral nutrition supplementation for 14 days may increase plasma prealbumin level, arm circumference, body weight, body mass index and may decrease plasma ammonia level in liver cirrhosis patients. BCAA enteral supplementation could not provide significant improvement of Fischer ratio, psychometric test, and electroencephalography for liver cirrhosis patients in this study. The prevalence of subclinical hepatic encephalopathy in this study is 32%.

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